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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/718,717	11/22/2000	Aya Jakobovits	ABGX-001CON3	5842

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EXAMINER
MCKELVEY, TERRY ALAN

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/23/2003 16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/718,717	Jokobovits et al.	
	Examiner	Art Unit	
	Terry A. McKelvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-8,11 and 12* is/are pending in the application.

4a) Of the above claim(s) *8* is/are withdrawn from consideration.

5)☒ Claim(s) *11 and 12* is/are allowed.

6)☒ Claim(s) *2-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/11/03 has been entered.

Election/Restrictions

Claim 8 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 4, filed 6/28/01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a mammalian cell having about a 55 kb deletion, does not reasonably provide enablement for making a deletion in the entire range of 15 kb to 3000 kb. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. This rejection is maintained for reasons of record set forth in Paper No. 6, mailed 9/7/01 and Paper No. 9, mailed 6/26/02. Applicants' arguments filed 7/11/03 have been fully considered but they are not deemed to be persuasive.

Response to Arguments

The applicant argues that the instant specification provides ample guidance for one of skill in the art to practice the invention without undue experimentation. This argument is not persuasive because the guidance is merely the general teachings like that in the prior art for doing deletions using a replacement targeting construct and positive selection. There

is nothing in the guidance of the instant application that specifically teaches how to predictably obtain the deletions in the range of up to 3000 kb. The single working example is at the very low end of the range. There is nothing in either the guidance in the specification or the working example in the specification which teaches how to overcome the art-recognized unpredictability of making very large deletions using a replacement targeting construct and positive selection, much larger than the mere 55 kb deletion made in the working example.

The applicant argues that Ramerez-Solis does not support a conclusion of lack of enablement because he did not have access to the instant specification, which was not publically available when the Ramirez-Solis reference was published. It is argued that he did not state that it is not possible to generate larger deletions using the method described in the instant specification. This argument is not persuasive because there is nothing about the method described in the instant specification that is any different from the prior art teachings concerning using a replacement targeting construct to generate deletions except in the instant application, there is an unsubstantiated assertion that the method can be used to generate extremely large deletions, much larger than ever achieved before and much larger than the single working example of a deletion that is

only a little larger than the largest prior art deletion. Thus, the lack of access to the teachings of the instant application did not affect what Ramirez-Solis teaches at all because the instant application adds no real guidance as to how to overcome the well known prior art limitations as to the size of deletion that can be generated using the method such as that taught by both the prior art and the specification. Therefore, the teachings of Ramirez-Solis does support a conclusion of lack of enablement because he teaches the same method as taught by the instant application, but with a teaching of the well known deletion limitation.

The applicant argues that Kimber et al states that replacement-type targeting was used to produce 100-200 kB deletions and thus this reference, using the claimed method, generated deletions of approximately 150 kb and accordingly, those skilled in the art, given the guidance provided in the instant specification, could readily generate deletions in the recited size range. This argument is not persuasive because Kimber et al used both positive and negative selection, as was previously indicated in the prior Office Action. The applicant goes on to argue in response that the instant application indicates that positive or negative selection can be used and thus Kimber used the procedures as disclosed and claimed in the

instant application. This argument is not persuasive because the claims are not directed to making gene deletion using the positive and negative selection method. The claims are only directed to the standard positive selection method which uses different steps and very different vectors from the positive and negative selection method and in which the integration of the vector itself causes the deletion. The positive and negative selection method, which is taught, for example, by Brenner et al (WO 94/21787) of record (the IDS filed 9/3/02) uses a two step approach, using homologous recombination to insert a vector into a site, the integrants are selected by positive selection (and no deletion is yet present), followed by a negative selection to select for cells in which the integrated vector was deleted out, resulting in a genomic deletion. See Figure 1 of Brenner et al which shows the constructs at each step. The fact that the application also indicates that positive or negative selection can be used has no bearing on the instant claims because only the very different positive selection is claimed. If positive and negative selection was being claimed, then Brenner et al would appear to be applicable as prior art because this reference teaches making extremely large deletions using that method (see page 15 of the reference).

In fact, as further evidence of the unpredictability of making very large deletions using the claimed positive selection method, Brenner et al specifically compares the two methodologies (standard targeting using positive selection and their invention of positive and negative selection), teaching the following:

"Relatively small deletions (500 bp to 15 kb) can be achieved in a defined manner. Such small deletions can also be achieved by standard targeting methodology, by choosing target regions for recombination that are separated by the desired deletion. If standard methodology is used, however, a positive marker must then be tolerated in the final locus. When no extra marker is desired in the final locus, then the method of this invention will permit one to effect a deletion without leaving any exogenous sequences.

Large deletions, up to 4000 kb, can be achieved by the methodology of this invention. The size of deletions that can be made by standard methodology are restricted and vary in efficiency. The method of this invention is far more powerful than conventional techniques, because it relies, not on intermolecular homologous recombination for the excision step, but rather upon intrachromosomal recombination, using negative selection. Large deletion events resulting from the subject

invention are more likely to occur at frequencies within the scope of a typical experiment, as compared to a deletion event resulting from a standard targeting experiment." (pages 15-16).

This passage of Brenner et al further supports the unpredictability of making very large deletions as instantly claimed. Another reference, Bradley et al (U.S. Patent No. 6,461,818 B1), also further supports the lack of enablement for the full scope of the claimed invention. This reference teaches: "Although conventional gene targeting technology in embryonic stem (ES) cells can generate virtually any type of mutation, including deletions of up to 20 kb, it has not been possible to delete substantially larger fragments by using standard methodology." (column 2, lines 6-10). Thus, the three cited references all support the unpredictability and lack of enablement of the full range of the claimed invention.

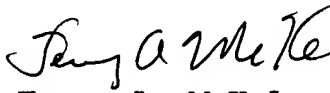
Therefore, in light of all available evidence, including the rejection set forth in the previous Office Actions, maintained above, the applicant's arguments, and the arguments set forth above and in the previous Office Actions, the claimed invention is still not considered to be enabled for the full, claimed scope and thus the rejection under 35 USC 112, first paragraph is properly maintained.

Conclusion

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

September 21, 2003